Cancer Chemother Pharmacol (1991) 28: 217–219
034457049100088Y

Cancer Chemotherapy and Pharmacology

Case report of metastatic familial pheochromocytoma treated with cisplatin and 5-fluorouracil

Vichien Srimuninnimit and Galen L. Wampler

Division of Hematology/Oncology, Department of Medicine, Medical College of Virginia, Richmond VA 23298, USA

Received 23 January 1991/Accepted 14 March 1991

Summary. We report on a rare case of malignant pheochromocytoma in a patient with a family history of this disease. After three cycles of treatment with cisplatin and 5-fluorouracil, a decrease in the need for antihypertensive treatment occurred, which lasted almost 2 years despite the discontinuation of chemotherapy. The patient showed an objective response, which was technically a minor response, although in this slow-growing tumor it was of major clinical significance. This chemotherapy regimen may play a role in the management of malignant pheochromocytoma.

Introduction

Malignant pheochromocytoma is a rare neoplasm of catecholamine secretory tissue that arises from the chromaffin cells of the sympathoadrenal system. There are no distinguishable chemical, biochemical or histopathological features by which benign lesions can be differentiated from malignant tumors. The only acceptable criteria are the presence of tumors in sites in which chromaffin cells are not usually found and the occurrence of visceral metastases [14]. The incidence of malignant pheochromocytoma has been reported to be as low as 5% and as high as 46% in different series [10–12].

About 10% of pheochromocytoma cases are familial and these are usually benign. Several distinct familial syndromes are described, including (1) neurofibromatosis and von Hippel-Lindau disease; (2) multiple endocrine neoplasia (MEA II), which involves pheochromocytoma associated with medullary carcinoma of the thyroid and parathyroid hyperplasia; and (3) familial pheochromocytoma, which does not involve other endocrine organs. Familial pheochromocytomas are expressed at an early age, may exhibit bilateral adrenal involvement, and are autosomal-dominantly inherited with high penetrance [4]. Malignant pheochromocytoma is thought not to occur in MEA syndrome [9], and there are apparently no reports of malignancy in patients with familial pheochromocytoma [3, 4, 8]. We report on a patient with a family history of pheochromocytoma who developed distant metastases at 10 years after primary treatment.

Offprint requests to: G. L. Wampler, Box 230, MCV Station, Richmond, VA 23298, USA

Case report

The patient was a white woman who first developed hypertension in 1967. In 1971 at the age of 26 years she experienced eclampsia during her second pregnancy and the hypertension did not resolve after a cesarean section had been performed. The urinary catecholamine level was >1,000 μg/24-h urine specimen (normal value <120 μg/24-h urine specimen) and angiography revealed a mass in the right adrenal gland. A right adrenalectomy was done and confirmed the diagnosis of adrenal pheochromocytoma. After surgery, urine catecholamines recovered to normal levels. The patient's mother, brother, son, and nephew all had had or subsequently developed pheochromocytoma.

In 1980 hypertension reoccurred. Urinary catecholamines, as well as an abdominal computerized tomographic scan (CT) and radiographs of lungs (CXRs), were within normal limits. In 1982, the urinary catecholamine level was 623 μg/24-h urine specimen, the vanillylmandelic acid (VMA) value was 11 mg (normal, 1–11), and CXRs as well as a chest CT revealed multiple nodules bilaterally. An abdominal CT showed no abnormality. Open lung biopsy on April 28, 1982, confirmed metastatic malignant pheochromocytoma.

In 1983 the patient developed lower back pain. A lumbar spinal CT demonstrated a large lytic defect in the posterior aspect of L-4, with a tumor mass involving the spinal canal. Radiation (3,600 cGY) was given for palliation. From 1982–1986, her hypertension was controlled with metyrosine given in doses increasing from 1 to 3 g/day. In 1986 a spinal CT showed bone metastases at T-8, the sacrum, and the right lower rib cage. A CXR revealed slight enlargement of the pulmonary nodules, and palliative irradiation was carried out. In 1987, 20 mg phenoxybenzamine daily was added for blood pressure control. In 1988, magnetic resonance imaging (MRI) of the spine demonstrated progressive involvement of the tumor on the spinal canal at irradiated areas T-8 and L-4 and destructive lesions at T-4, T-12, and the sacrum.

Chemotherapy was begun in April 1988 and consisted of 100 mg/m^2 cisplatin given on day 1 by i.v. infusion over 2 h along with appropriate hydration, antiemetics, and 12.5 g mannitol, followed by 900 mg/m^2

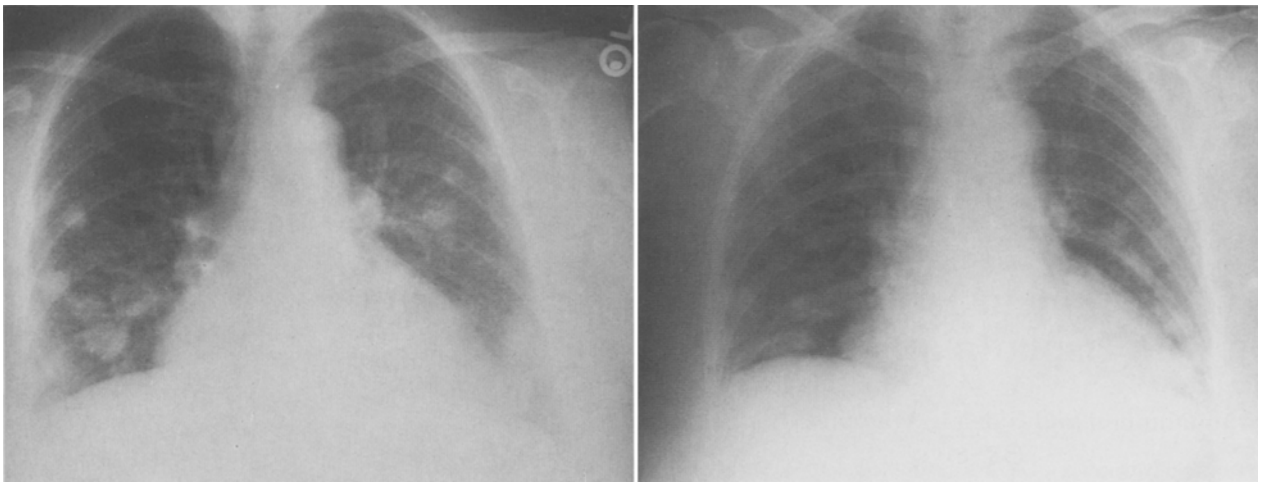

Fig. 1. Chest radiographs obtained on January 29, 1988, before treatment and on June 13, 1988, after one cycle of chemotherapy (maximal response). Lesions showed a variable decrease in size, some representing >50% but most being <50% in area measurement. Response was maintained until January 1990, at which time the lesions appeared to have become significantly larger on X-ray examination

5-fluorouracil (5-FU) given daily by continuous infusion for 5 days (120 h). The patient received another two cycles of cisplatin and 5-FU in June and August of 1988. A CXR showed only a minor response of the lung lesions (Fig. 1), and the spinal MRI revealed only a slight decrease in the L-4 lesion, but the subject's hypertension could be controlled with a decreased dose of 500 mg metyrosine daily (Fig. 2). Chemotherapy was stopped due to stable disease. The patient, who was totally bedridden before undergoing chemotherapy, became ambulatory.

In April 1989, anterior retroperitoneal L-4 vertebrectomy and fusion were performed for back pain related to L-5 nerve root compression. Surgery had not been done earlier due to the poor condition of the patient. Pathological examination showed malignant pheochromocytoma metastatic to the L-4 vertebra. In January 1990, a CXR revealed a slight increase in the size of multiple lung metastases, but the patient showed no chest symptoms. She was ambulatory and had been taken off most of her narcotic drugs, and her blood pressure was controlled with 1 g metyrosine daily. By March 1990, back pain had recurred and the patient was placed on the CVD regimen (cyclophosphamide, vincristine, and dacarbazine) because of the previously reported high response [1]. The total remission duration for cisplatin and 5-FU treatment was 20 months.

The patient received three cycles of CVD chemotherapy from March until June of 1990 without showing an objective response; because of increasing pain and metyrosine dose (1,500 mg/day), she was then given three additional cycles of 5-FU/cisplatin between September and November of 1990, but no objective response was observed. As of February 1991, the patient has been treated with only 325 mg acetaminophen and 30 mg codeine for pain along with 500 mg metyrosine daily to control her blood pressure.

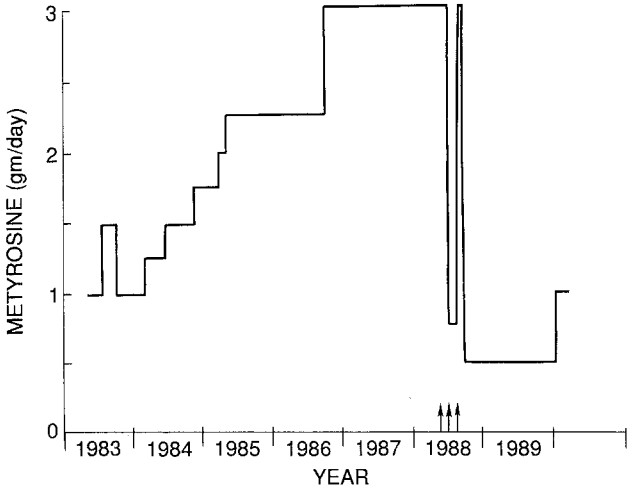

Fig. 2. Metyrosine dosage by time. Prior to the start of metyrosine administration, the blood pressure had been controlled with 160 mg inderal and 25 mg hygroton daily; 1,500 mg aldomet daily was added for the last 3 months. *Arrows* indicate the timing of the three cisplatin/5-fluorouracil treatments. The patient also received 10–20 mg phenoxybenzamine daily from February 1988 until August 1988, both prior to and during chemotherapy

Discussion

The natural history of malignant pheochromocytoma is variable, and long-term survival can sometimes be achieved without specific antineoplastic therapy. Survival data on patients with malignant pheochromocytoma are difficult to assess because of the rarity of the tumor. Patients exhibiting metastases did not develop them until 0.2–28.7 years after their initial surgery. The incidence of detection for the first 9 years was 5%/year [9]. The average interval from diagnosis of the primary tumor to the discovery of bone metastases was 6.5 years, which indicated that even malignant pheochromocytoma tends to grow slowly [7]. Some patients lived for >10 years after the discovery of bone metastases; the 5-year survival rate was 36%. The majority of patients who died of malignant pheochromocytoma did so within 3 years after the appearance of metastases [6, 16].

The common sites of metastases include the lymph node, bone, lung, and liver; the most common site is bone, with the axial skeleton predominating. Bone scan and CT are the most sensitive modalities for the detection of bone metastases, discovering 74% and 71% of metastases, respectively. Metaiodobenzylguanidine tagged with iodine 131 ([^{131}I]-MIBG) can also detect recurrent or metastatic pheochromocytoma; its sensitivity varies from 55% to 87%, but its specificity approaches 100% [7, 13]. Some investigators recommend yearly evaluations using [^{131}I]-MIBG for all patients following resection of pheochromocytoma [2].

Our patient was unusual in that she had metastatic pheochromocytoma and her disease is familial. Although several familial patients have required reoperation for recurrent tumors, in no case did the behavior of the latter otherwise suggest metastatic malignancy [7], in contrast to our case.

The basic principles in the treatment of malignant pheochromocytoma involve the surgical resection of recurrences or metastases whenever possible and the treatment of hypertensive symptoms with alpha- and beta-adrenergic blockade or metyrosine, an inhibitor of catecholamine synthesis. Radiation can palliate painful skeletal metastases. The role of [^{131}I]-MIBG in the treatment of metastatic pheochromocytoma is disappointing due to the lack of an appreciable uptake of [^{131}I]-MIBG by the tumor [9].

The role of chemotherapy in the management of pheochromocytoma is poorly defined. Most reports involve single cases or small series. Combination chemotherapy with cyclophosphamide, vincristine, and dacarbazine (CVD) has been reported to produce a high objective response rate [1, 5, 15], with a complete and partial (objective) response rate of 57% being obtained in 14 patients [1]. In addition, there were 3/14 minor responses and 2/14 cases of stable disease [1]. The median duration of responses was 21 months, with inprovement in the performance status and blood pressure being noted in responding patients, including those showing only minor responses [1].

In the present case, hypertension and pain became more easy to control after the patient had received chemotherapy. The treatment appeared to have a definite impact on the natural history of her disease, although the objective tumor response was insufficient to represent a partial response. It would appear that this combination would be suitable for further testing.

References

1. Averbuch SD, Steakley CS, Young RC, Gelmann EP, Goldstein DJ, Stull R, Keiser HR, Beierwaltes WH (1988) Malignant pheochromocytoma: effective treatment with a combination of cyclophosphamide, vincristine, and dacarbazine. Ann Intern Med 109: 267
2. Beierwaltes WH, Sisson JC, Shapiro B, Lloyd RV, Dmuchowski C, Rabbani R (1986) Malignant potential of pheochromocytoma (P): implications for follow-up (abstract). Proc Am Assoc Cancer Res 27: 156
3. Glowniak V, Shapiro B, Sisson JC, Thompson NW, Coran AG, Lloyd R, Kelsch RC, Beierwaltes WH (1985) Familial extra-adrenal pheochromocytoma: new syndrome. Arch Intern Med 145: 257
4. Irvin GK, Fishman LM, Sher JA (1983) Familial pheochromocytoma. Surgery 94: 938
5. Keiser HR, Goldstein DS, Wade JL, Douglas FL, Averbuch SD (1985) Treatment of malignant pheochromocytoma with combination chemotherapy. Hypertension 7 Part II: I–18
6. Lewi HJ, Reid R, Mucci B, Davidson JK, Kyle KF, MacPherson SG, Semple P (1985) Malignant pheochromocytoma. Br J Urol 57: 394
7. Lynn MD, Braunstein EM, Wahl RL, Shapiro B, Gross MD, Rabbani R (1986) Bone metastases on pheochromocytoma: comparative studies of efficacy of imaging. Radiology 160: 701
8. May AG, Moss A, Gutierrez OH, Burday SZ, Campbell RG (1981) Clinical study of pheochromocytoma. Am J Surg 1141: 346
9. Norton JA, Doppman JL, Jensen RT (1989) Cancer of the endocrine system. In: DeVita VT Jr, Hellman S, Rosenberg SA (eds) Cancer: principles and practice of oncology, 3rd edn. J. B. Lippincott, Philadelphia, p 1269
10. Samaan NA, Hickey RC (1987) Pheochromocytoma. Semin Oncol 14: 297
11. Scott HW, Halter SA (1984) Oncologic aspects of pheochromocytoma: the importance of follow-up. Surgery 96: 1061
12. Scott HW, Reynolds V, Green N, Page D, Oates JA, Robertson D, Roberts S (1982) Clinical experience with malignant pheochromocytomas. Surg Gynecol Obstet 154: 801
13. Shapiro B, Copp JE, Sisson JC, Eyre PL, Wallis J, Beierwaltes WH (1985) Iodine-131 metaiodobenzylguanidine for the locating of suspected pheochromocytoma: experience in 400 cases. J Nucl Med 26: 576
14. Sherwin RP (1964) Present status of the pathology of the adrenal gland in hypertension. Am J Surg 107: 136
15. Siddiqui MZ, Eyben FE, Spanos G (1988) High-voltage irradiation and combination chemotherapy for malignant pheochromocytoma. Cancer 62: 686
16. Van Heerden JA, Sheps SG, Hamberger B, Sheedy PF, Poston JG, Remine WH (1982) Pheochromocytoma: current status and changing trends. Surgery 91: 367